Glomerulonephritis may occur with bacterial shunt nephritis or bacterial endocarditis. Black and co-workers[13] first described the cases of two patients with nephrotic syndrome in whom control of ventriculoatrial shunt infection was followed by resolution of the glomerulonephritis. Subsequent experience has shown that as many as 27% of cerebrospinal shunts become infected, usually with *Staphylococcus epidermidis*,[14,15] but the incidence of glomerulonephritis in infected patients is less than 5%.[15,16] Hypocomplementemic glomerulonephritis has occurred in patients with chronic, untreated infections as was the case in this patient.[15] The most common clinical manifestations of glomerular involvement are proteinuria and hematuria with nephrotic syndrome present in as many as 29% of cases.[16] The renal lesion most frequently associated with shunt nephritis is a type 1 membranoproliferative glomerulonephritis with diffuse granular deposition of IgG, IgM and C3.[15-18] Depressed complement levels, elevated C1q binding levels and the finding of bacterial cell wall products in glomeruli have supported an immune complex origin for the glomerulonephritis. In our patient, the presence of erythrocyte casts, elevated C1q binding level and decreased complement levels support a diagnosis of shunt nephritis. Unfortunately, further characterization of the glomerulonephritis by immunofluorescence was not obtained as the biopsy specimen yielded insufficient tissue for immunofluorescent staining.

Replacement of infected shunts has usually been necessary for the resolution of shunt nephritis.[13-20] After shunt removal in our patient, the C1q binding level fell rapidly and complement levels rose. Renal function returned to normal ten months after initiation of antituberculous therapy and replacement of the shunt. At least nine months elapsed between the development of the infection and its diagnosis. This case shows that the diagnosis of shunt nephritis may be missed initially even when infection caused by more common pathogens is sought. Clinical, laboratory and renal pathologic data suggest that this represents a case of shunt nephritis due to mycobacterial infection.

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Somatostatinoma—
The Most Recently Described Pancreatic Islet Cell Tumor

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A 51-YEAR-OLD WOMAN was found with electron microscopy to have metastatic lesions in the liver and immunohistochemical characteristics of somatostatinoma. The concentration of somatostatin in her blood was elevated, as was the calcitonin concentration although calcium, gastrin, adrenocorticotropic hormone (ACTH) and cortisol levels were within normal range. With the establishment of a diagnosis of somatostatinoma, streptozocin was chosen for therapy rather than fluorouracil and doxorubicin, which had previously been administered. We review the 11 previous cases of this tumor, which had been designated as producing the "inhibitory syndrome." With the current availability of specific antisera to entopic and ectopic islet cell hormones and the use of electron microscopy, more such tumors may be recognized. The ultimate goals of such a search are to detect tumors before metastasis has occurred and to indicate the most appropriate chemotherapy.

Report of a Case

In 1978 a 47-year-old woman presented at St. Paul's Hospital (Vancouver, British Columbia) with hypertension. On physical examination no correctable cause was found but hepatomegaly was present. She had no diabetes, her weight had remained unchanged and she had no evidence of malabsorption. She had taken oral contraceptives for eight years. Labo-

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ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
5-HIAA = 5-hydroxyindoleacetic acid
VIP = vasoactive intestinal polypeptide
VMA = vanillyl mandelic acid

ratory values included a test positive for infectious mononucleosis and abnormalities on liver function studies. In 1979 persistently abnormal liver function values and a liver scan that showed filling defects led to a liver biopsy. The biopsy specimen showed cellular infiltrates with multiple angiomata. Serum calcium and gastrin levels were normal. A celiac arteriogram showed multiple adenomata. An upper gastrointestinal x-ray series showed external compression of the stomach. No specific therapy was given. In 1980 a second liver biopsy was done at the time of cervical dilatation and uterine curettage. The pathologic diagnosis was angiofibromata.

The following year, diabetes was diagnosed and painful osteoblastic metastatic lesions appeared in the pelvic bones. A regimen of fluorouracil and doxorubicin hydrochloride was initiated. A bone marrow aspirate taken in November 1981 contained malignant cells. A 24-hour test for urinary vanillyl mandelic acid (VMA) gave a value of 4.2 mg (normal, 0 to 7.5); a test for 5-hydroxyindoleacetic acid (5-HIAA) was negative. Repeat tests for serum gastrin and calcium showed no abnormalities. A laparotomy failed to show a primary pancreatic lesion. Computed tomographic scan and ultrasound confirmed extensive hepatic metastasis but no pancreatic tumor was found. In April 1982, electron-microscopic studies of the hepatic metastatic lesions showed intracellular granules characteristic of somatostatinoma; antisera to several islet cell hormones, including insulin and glucagon, gave positive staining for somatostatin only (Figure 1). The patient was not obese and was not taking insulin or oral hypoglycemic agents.

A blood specimen drawn while the patient was fasting, four days after the beginning of a course of streptozocin (750 mg per day for five days), contained 250 femtomol per ml of somatostatin (normal, 120 ± 80 for two standard deviations), 186 pg per ml of calcitonin (normal, 0 to 60) and 48 pg per ml of adrenocorticotropic hormone (ACTH; normal, 50 to 150); serum cortisol was 25.8 μg per dl (normal, 8 to 28), calcium 8.7 mg per dl (normal, 8.6 to 10.3), glucose 151 mg per dl (normal, 65 to 110) and phosphorus 2.4 mg per dl (normal, 2.5 to 4.4). Serum total protein was 5.5 and albumin 3.5 grams per dl; aspartate aminotransferase (formerly, SGOT) 82, lactic dehydrogenase 204 and alkaline phosphatase 579 units per liter (normal, 20 to 90). Prolactin was 24.2 ng per ml (normal, 0 to 20). A sella turcica x-ray series was normal. A brief episode of diarrhea in April 1982 was followed by constipation. No studies were done on the diarrheal fluid as the patient was not in hospital. She has had no symptoms specific for gallbladder disease. When last seen in 1983, the patient was doing well and was experiencing no bone pain. She had been taking streptozocin for four months. Hepatomegaly was decreasing as evaluated clinically.

Laboratory Studies

The bone marrow specimen was fixed in Zenker's fixative and the liver biopsy tissue in formalin for light-microscopic and immunoperoxidase studies. A portion of the liver tissue was recovered from the paraffin block, postfixed in 2% osmic acid and embedded in epoxy resin (Araldite) for electron-microscopy. The hormone content of the tumor was determined by the peroxidase-antiperoxidase technique of Sternberger and associates,[1] using carbozol adapted for measuring somatostatin, insulin, gastrin, glucagon and vasoactive intestinal polypeptide (VIP). The study was done by Anne Worth, MD, of the Cancer Control Agency of British Columbia, Vancouver, BC.

The specimen of the needle liver biopsy done in 1979 showed sheets of small cells with uniform nuclei and scant

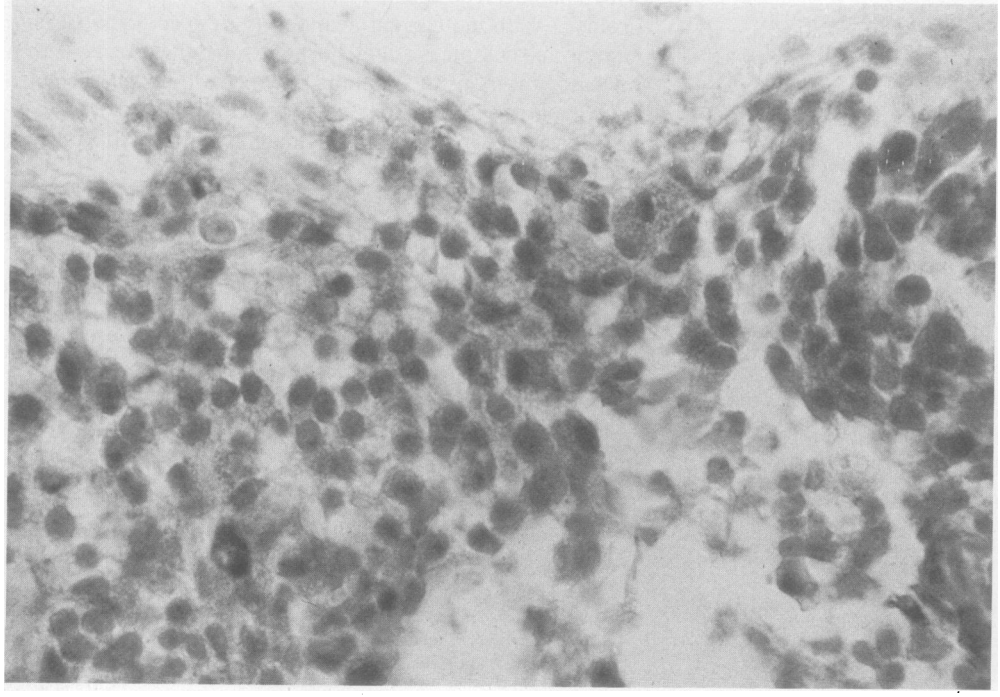

Figure 1.—Immunohistochemical study of the hepatic metastasis showing cytoplasmic somatostatin (see text for method).

cytoplasm separated by large irregular zones of hyalinized fibrous tissue containing calcium deposits. The bone marrow biopsy specimen from November 1981 contained focal peritrabecular metastasis. The tumor had an organoid architecture composed of cells with abundant eosinophilic cytoplasm, uniform small nuclei and no mitotic activity. The trabecular bone abutting the tumor was thickened from pronounced osteoblastic activity. Electron-microscopic studies of the liver biopsy specimen taken in January 1982 showed tumor cells containing small, membrane-limited, uniform, electron-dense granules (200 to 400 nm). Cell ultrastructure, however, was poorly preserved because of formalin fixation. The cell cytoplasm stained strongly with antibody to somatostatin (Figure 1) and was negative for gastrin, glucagon, insulin and VIP by the peroxidase-antiperoxidase technique.

Somatostatin concentration in plasma specimens was measured for us by T. Yamada, MD (Center for Ulcer Research and Education [CURE], Wadsworth VA Medical Center, Los Angeles), using the method of Yamada and co-workers[2] with modification for measuring somatostatin in plasma using antibody 1001.[3] The specimen was stored on ice using aprotinin as a proteolytic inhibitor. Serum prolactin, calcitonin, gastrin and plasma ACTH levels were measured by D. Bednarczyk, PhD, and G. E. Wilkins, MD, at St Paul's Hospital, Vancouver, BC, by standard radioimmunoassay techniques. Urinary VMA and 5-HIAA levels were measured by routine laboratory techniques.

Discussion

Somatostatin is a cyclic tetradecapeptide with a molecular weight of 1,600. It can be found in the hypothalamus, pancreas, stomach, duodenum and jejunum when these organs are studied by specific radioimmunoassay. Specimens of these organs and the thyroid will produce a stain positive for somatostatin by immunohistochemical techniques. The inhibitory activities of somatostatin are widespread and when it is secreted in excessive amounts it produces the "inhibitory syndrome." Although its full physiologic role has not been completely determined, it is known to suppress pituitary release of growth hormone[4] and thyroid-stimulating hormone,[5] pancreatic release of insulin and glucagon,[6] K-cell release of gastrin[7] and intestinal mucosal release of cholecystokinin[8] and secretin.[9,10] Its effects are not confined to the endocrine system, however, as it inhibits secretion of the enzymes amylase, chymotrypsin, trypsin and pepsin[9] and of gastric acid and pancreatic bicarbonate.[7,10]

Within the pancreatic islet somatostatin has a major effect on carbohydrate metabolism via a paracrine influence[11]: the δ-cell produces somatostatin, which inhibits β-cell output of insulin. Insulin from β-cells inhibits the secretion of glucagon in α-cells, whereas glucagon stimulates both insulin and somatostatin production. The blood glucose concentration is a consequence not only of nutrient intake but also of the dynamic equilibrium between the opposing hormones within the islet and at the level of peripheral tissue.

Studies using somatostatin infusion have shown that when it suppresses insulin and glucagon release in normal humans, hyperglycemia may not occur unless glucagon is infused. Gerich and associates[6] found that somatostatin suppression of glucagon release prevented ketoacidosis, yet Lundbaek and colleagues[12] noted that somatostatin suppression of glucagon release did not correct previously established ketoacidosis. Felig and co-workers[13] concluded on the basis of studies with somatostatin infusion that glucagon may worsen the consequences of insulin deficiency but is neither sufficient nor necessary for the development of diabetes.

Significant ketosis can be a finding in patients with somatostatinoma. Axelrod and colleagues[14] found a graded relationship between the plasma somatostatinlike immunoreactivity level and the biologic effects of endogenous somatostatin produced by an islet cell tumor. They concluded that the relationship in humans between the plasma somatostatinlike immunoreactivity level and its biologic effect, such as inhibition of arginine-induced glucagon and growth hormone secretion, is different for different hormones. Furthermore, mild fasting hyperglycemia was present in patients despite inhibition of glucagon release, so that hyperglucagonemia is not required for the occurrence of fasting hyperglycemia, and

TABLE 1.—*Some Clinical and Pathologic Features of Somatostatinoma*

Case	References	Age, Years	Sex	Primary Pancreas	Metastasis in: Liver	Bone	Other	Gallbladder Disease	Diabetes	Anemia	Hypertension	Diarrhea or Steatorrhea	Other Hormone Excess	Survival
1. . .	Larsson et al, 1977[15]	55	♀	+	+	−	. .	+	+	−	NS	+	. .	Few hours post-operatively
2. . .	Ganda et al, 1977[16]	46	♀	+	−	−	. .	+	+	+	−	−	. .	4 years (SA)
3. . .	Kovacs et al, 1977[17]	54	♂	+	+	−	. .	NS	+	NS	+	−	ACTH	6 days post-operatively
4. . .	Pipeleers et al, 1979[18]	63	♀	+	+	−	. .	+	+	+	NS	+	. .	30 weeks (SA)
5. . .	Kjejs et al, 1979[19]	52	♂	+	+	−	. .	+	+	+	−	+	Calcitonin	10 months (SA)
6. . .	Penman et al, 1980[20]	33	♀	+	+	−	Nodes	−	*	NS	NS	NS	Insulin	NS
7. . .	Penman et al, 1980[20]	36	♂	+	−	−	. .	−	+	NS	NS	NS	ACTH	2 years (SA)
8. . .	Galmiche et al, 1980[21]	70		+	+	−	Duodenum	+	+	−	−	+	Calcitonin	4 weeks post-operatively
9. . .	Bloom and Polak, 1980[22]	NS	NS	+	−	−	. .	NS	+	NS	NS	+	. .	. .
10. . .	Asa et al, 1980[23]	68	♀	+	+	−	Nodes	NS	+	+	−	+	Endorphin, Calcitonin, ACTH, gastrin	20 months
11. . .	Axelrod, 1981[14]	54	♀	+	+	+	Kidney, adrenal, thyroid, skin, ovary	+	+	+	−	+	. .	15 months
12. . .	Reynolds et al, 1985	51	♀	?	+	+	. .	−	+	+	+	+	Calcitonin, PRL ±	5 months (SA)

+ = yes, − = no, NS = not stated, SA = still alive at time of report, ACTH = adrenocorticotrophic hormone, PRL = prolactin

*Patient had hypoglycemia.

significant ketosis can occur. When our patient was fasting, the serum glucose value was in the range of 140 to 170 mg per dl and there was no evidence of ketosis. She was not obese. Unfortunately, plasma insulin and glucagon levels were not measured due to a technical problem. We assume that the elevated level of circulating somatostatin caused suppression of insulin and glucagon release, a phenomenon that has been shown repeatedly by others.

Somatostatinomas are apparently extremely rare, only 11 cases having been reported.[14-23] In Table 1 the major clinical and pathologic features of these cases and of our own are set forth. The case of deNutte and co-workers[24] seems to be the same as that of Pipeleers and colleagues,[18] and that of Wright and associates[25] is included in the report of Penman and colleagues.[20] Pancreatic islet cell tumors can be divided into those that produce entopic hormones and those that produce ectopic hormones.[26] The first category includes the insulinoma (hypoglycemia syndrome),[27] glucagonoma (diabetes-dermatitis syndrome),[28] somatostatinoma (inhibitory syndrome), pancreatic polypeptidoma (no characteristic syndrome but pancreatic polypeptide serves as a marker for diarrheogenic and ulcerogenic syndromes)[29] and the very complex carcinoid islet-cell tumor (atypical carcinoid syndrome).[30] The second category includes the pancreatic gastrinoma (ectopic ulcerogenic syndrome),[31] vasoactive intestinal polypeptidoma (watery diarrhea-hypokalemia-achlorhydria syndrome of Verner and Morrison),[32] corticotropinoma (ectopic ACTH syndrome),[33] parathyrinoma (ectopic hypercalcemia syndrome),[34] vasopressinoma (ectopic syndrome of inappropriate antidiuretic hormone)[29] and ectopic cholecystokininoma (syndrome of diarrhea with excess gastric acid but without ulceration).[35] The presence of hypertension in one previous case and in the current case may be coincidental, considering the prevalence of hypertension in the general population.

The simple concept of one hormone of tumorous origin giving rise to one clinical or biochemical problem must give way to new ideas: a pancreatic tumor can secrete many hormones, leading to many problems; it can elaborate a single hormone creating many problems, and the pattern of hormone secretion and the biologic response to those hormones can change with time. Of the 11 somatostatinoma cases in the literature, gallbadder dysfunction (representing inhibition of cholecystokinin) was present in six, steatorrhea or diarrhea in seven, diabetes (representing inhibition of insulin release) in ten and hypochlorhydria (representing inhibition of gastrin) in three. In association with hypersomatostatinemia, three patients have had elevated ACTH levels,[17,20,23] one had hyperinsulinemia causing hypoglycemia,[20] four (including our own) had hypercalcitoninemia,[19,21,23] and one had elevated calcitonin, ACTH, gastrin and α-endorphin levels.[23] The mechanism by which anemia has occurred in some cases is uncertain, although it may be via erythropoietic suppression. Because of the presence of M-protein and metastatic lesions to bone, one case was diagnosed and treated as multiple myeloma before the correct diagnosis was reached.[14] The mild elevation of the prolactin level in our case may or may not be significant. No conclusion can be drawn as only one measurement was done, and that measurement can be considered normal for the luteal phase of the menstrual cycle.

In our case, the primary site has not yet been identified, but in all of the previous cases, the primary was a single pancreatic lesion ranging in size from 0.5 to 20 cm. We did not do a pancreatic arteriogram or get a transhepatic portal venous hormone specimen. Hepatic metastasis had occurred in 9 of the previous 11 cases, as well as in ours. Our case is the second with bone metastasis but the first to be reported with osteoblastic, rather than osteolytic, lesions.[14] Some cases were discovered at the time of a cholecystectomy. Our patient presented with hepatomegaly, abnormal findings of liver function tests and filling defects on the liver scan. Initially, therapy was started with a regimen of fluorouracil and doxorubicin but when the diagnosis of pancreatic endocrine tumor was established it was changed to streptozocin. Previous cases have been treated by radical pancreatoduodenectomy,[13,14,20] enucleation[19] or by biopsy and streptozocin therapy.[14,19] One patient's disease had infiltrated to the pancreas with metastasis to liver and peritoneal lymph nodes, so only biopsy was done. Treatment postoperatively was with benzothiadiazine and fluorouracil.[19]

It is unclear what combination of features should lead to a concerted effort to find somatostatinomas. With the widespread availability of localization techniques such as ultrasonography, computed tomography and arteriography, more such cases should be uncovered, provided that a physician applies these tests appropriately, even in cases of metastatic lesions. The presence of associated problems such as diabetes, diarrhea, anemia and cholecystic disease should be reason to pursue the diagnosis of a rare endocrine tumor. The ultimate goals of such a search would be to detect and classify the tumor at the earliest possible stage and to indicate the most appropriate chemotherapy.

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Accidental Dopamine in the Eye

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WE IN THE MEDICAL profession are frequently made aware of unusual and often unexpected side effects of commonly used drugs. These effects may appear either when the drug has been given in the usual manner or when the recommended dosage has been inadvertently exceeded. Occasionally an unanticipated reaction may arise when a drug is instilled via an unintended route. This may occur through the mucous membranes of the eye, which are capable of systemic drug absorption, as confirmed by recent reports of cardiovascular sequelae related to the use of pindolol, metoprolol and epinephrine eye drops.[1-3] In a review of reported systemic side effects of ophthalmic drugs in common usage before 1977, the use of at least one drug, phenylephrine, was found to be associated with several instances of serious untoward effects.[4] Persons working in chemical plants and laboratories know that the eyes are important areas for accidental drug contamination. I report a case of accidental instillation of dopamine in the eye of an intensive care unit nurse.

Report of a Case

A healthy 32-year-old woman, an intensive care unit nurse, accidentally splashed one or two drops of undiluted dopamine into her left eye while preparing a standard dilution for intravenous use. She dried the eye and continued to work until several minutes later when she noted the abrupt onset of dizziness, palpitations, facial flushing and a dry mouth. She went to the emergency room, where an electrocardiogram showed supraventricular tachycardia at a rate of 160 per minute with diffuse nonspecific ST-T abnormalities (Figure 1.) She was admitted to hospital for observation.

(Strauss R: Accidental dopamine in the eye. West J Med 1985 Mar; 142:397-398)

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Her medical history included mild hypertension of one year's duration, well controlled on a regimen of amiloride (5 mg) and hydrochlorothiazide (50 mg) every other day. She said she had no history of cardiac disease, rheumatic fever, heart murmur, chest pain, palpitations or dizziness and was receiving no other medications.

Findings of a physical examination were remarkable only for a pulse of 160 and a blood pressure of 152/100 mm of mercury. A cardiac examination done during periods of sinus rhythm showed no abnormalities. Laboratory results included normal values for blood count, electrolytes and free thyroxine. A standard M-mode echocardiogram was normal.

The patient's hospital course was characterized by spontaneously resolving periods of paroxysmal supraventricular tachycardia and intermittent sinus tachycardia, which gradually became less frequent. She was able to identify these as periods of flushing and palpitations. The episodes of tachycardia were not responsive to carotid sinus massage, but did revert on one occasion after she was given verapamil, 5 mg, intravenously. On the following day, an electrocardiogram was within normal limits (Figure 2). Except for fatigue and a fair amount of anxiety over the mishap, she was discharged in good condition on the third hospital day. Values for serum catecholamine and urine metanephrine obtained after her discharge were within normal limits.

Discussion

This case is a dramatic example of a seemingly innocuous amount of conjunctival contamination causing significant morbidity. It we estimate that there are ten drops per milliliter, one drop of undiluted dopamine (40 mg per ml) contains a dose of 4,000 μg. Assuming that only one drop contaminated the eye of this 65-kg woman, she received an approximate bolus of 60 μg per kg, not an inconsequential amount! There is little doubt that there was a direct causal relationship between the mishap and the ensuing events. Dopamine has well-known β-mimetic effects that could have been responsible for the tachycardia experienced by this woman.[5] When dopamine is given intravenously, its effect is gone within minutes. It was surprising to us that episodes of paroxysmal tachycardia continued for as long as 48 hours. This led us to exclude the possibility of underlying thyrotoxicosis, pheo-